Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.014

Peripartum Cardiomyopathy

Predictors of Recovery and Current State of Implantable Cardioverter-Defibrillator Use

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Objectives The purpose of this study was to identify the predictors of left ventricular (LV) recovery in patients with peripartum cardiomyopathy (PPCM) and to record rates of implantable cardioverter-defibrillator (ICD) use.

Background PPCM is a rare, life-threatening disease. The use of ICDs has not been clearly understood in this patient group. Identification of the predictors of persistent LV dysfunction can help select patients at risk for sudden cardiac death.

Methods A retrospective study was conducted at 2 academic centers between January 1, 1999, and December 31, 2012. Clinical and demographic variables and delivery records of patients with a diagnosis of PPCM (*International Classification of Diseases, 9th Revision* code 674.5) were reviewed. Improvement in LV function was noted from echocardiography reports.

Results The total sample comprised 100 patients, of whom 55% were African Americans, 39% were Caucasians, and 6% were Hispanic, with a mean age of 30 ± 6 years. Mean left ventricular ejection fraction (LVEF) at diagnosis was 28 ± 9%. Forty-two percent of patients showed improvement in LVEF over a mean duration of 33 ± 21 months. Postpartum diagnosis (hazard ratio: 3.0; $p = 0.01$) and Caucasian/Hispanic race (hazard ratio: 2.2; $p = 0.01$) were predictors of improvement in LVEF. Only 7 of the 58 patients (12%) who did not have improvement in their LVEF had an ICD implanted. There were 11 deaths, with a trend toward higher mortality in those who did not display improved LV function (15% vs. 5%; $p = 0.1$).

Conclusions More than one-third of women with PPCM improve LV function with delayed recovery noted in the majority of these patients. Caucasians and those diagnosed in the postpartum period appear to be the most likely to recover. The rate of ICD implantation for primary prevention of sudden cardiac death in this patient group is low. (J Am Coll Cardiol 2014;63:2831–9) © 2014 by the American College of Cardiology Foundation

Peripartum cardiomyopathy (PPCM) is a rare, idiopathic cardiomyopathy characterized by the development of systolic heart failure toward the end of pregnancy or in the months after delivery (1,2). The reported incidence shows significant geodemographic variation, from 1 in 500 live births in Haiti to 1 in 4000 live births in the United States (3–6). Identified risk factors for PPCM include multiparity, advanced maternal age, twins, preeclampsia, gestational hypertension, and African-American race (1,2,7–9).

Despite the recognition of this disease as a separate entity in 1937, the mortality rates are not yet well characterized (8–19), ranging from 4% to 50% (2,8–19). At least one-fourth of deaths in PPCM are sudden cardiac deaths presumed to be caused by ventricular tachyarrhythmias (16). Sudden cardiac death in these young women could potentially be averted by insertion of an implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy devices (CRTDs) may reduce progression to end-stage myocardial dysfunction. The American College of Cardiology Foundation/American Heart Association 2009 guidelines recommend implantation of an ICD for primary prevention of sudden cardiac death in all patients with ischemic and nonischemic cardiomyopathy with ejection fraction (EF) ≤35% in patients with New York Heart Association (NYHA) functional class II and III and EF <30% in patients with NYHA class I if there is no improvement in EF after 3 to 6 months of guideline-directed

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Manuscript received August 5, 2013; revised manuscript received March 8, 2014, accepted April 8, 2014.

JACC Vol. 63, No. 25, 2014
July 1, 2014:2831–9

Abbreviations and Acronyms

CRTD = cardiac resynchronization therapy device

ICD = implantable cardioverter-defibrillator

NYHA = New York Heart Association

PPCM = peripartum cardiomyopathy

optimal medical therapy (20). To date, no studies have reported the use of ICDs for primary prevention in this patient group. PPCM is also presumed to be associated with a higher likelihood of recovery of left ventricular (LV) function than cardiomyopathy attributable to other causes (2,10,17,19,21). Thus, prediction of who will recover from the disease helps determine who might best benefit from an ICD. Previous studies have shown that baseline LV EF >30%, LV end-diastolic diameter <5.5 cm, older age, and Caucasian race predicted recovery of LV function (22–29). However, either these were single-center studies with small sample sizes of ≤55 patients, or the information was obtained from other countries and surveys that were subject to ascertainment, recall, and selection bias or were not controlled for other covariates.

We thus wanted to study the mortality and LV recovery rates and examine ICD implantation rates at tertiary academic centers that offer a good mix of patients of different ethnicities. We sought to identify the predictors for LV recovery and the current rates of ICD use.

Methods

This was a retrospective study conducted at 2 large tertiary care academic centers, the University of Kansas (Kansas City, Kansas) and the Detroit Medical Center (Detroit, Michigan), where cardiovascular and high-risk pregnancy services are available. Approval was obtained from the institutional review boards at both institutions.

Patients

All patients >18 years of age who were diagnosed with postpartum/peripartum cardiomyopathy at the 2 centers were studied. The medical records of these patients were identified by use of International Classification of Diseases-9th Revision diagnostic codes for PPCM (674.50, 674.51, 674.52, 674.53, and 674.54) that were used for discharge diagnoses from the hospital or ambulatory clinic visits. At the University of Kansas, medical records were obtained for patients diagnosed between January 1, 2004, and August 31, 2010. At the Detroit Medical Center, records were obtained for patients who were diagnosed with PPCM between January 1, 1999, and December 31, 2010. All delivery records and follow-up encounters were reviewed for clinical and demographic information. Patients with a history of prior cardiomyopathy attributable to other causes or structural heart disease were excluded. Each patient was followed up until December 2012 for any improvement in EF. Time to recovery was noted for patients who had improvement in LV function. For those without any improvement in EF, the date of the last echocardiogram was used to measure the period during which no improvement in EF was observed. ICD implantation was also noted. All-cause mortality was obtained from the Social Security Death Index and confirmed by chart review when available. For mortality analysis, time to death was used for those who died, and December 2012 was used as the last follow-up date for all those who survived.

Assessment of EF. EFs at the time of diagnosis of PPCM were recorded and considered baseline EFs. Each patient was followed up over time to assess EF, and the EF from the last echocardiogram report was noted for those without LV improvement. For patients who had an improvement in EF, the EF and the time to improvement in EF were noted.

Definition of improvement. An EF >50% at follow-up was considered complete recovery. If the EF remained <35%, it was considered no improvement. If the follow-up EF was between 35% and 50%, the improvement was considered partial provided that there was a >10% absolute increase from baseline (e.g., from 35% to >45%). If patients had either partial or complete improvement, they were included in the "any improvement" category used for the analysis.

Statistical Analysis

Statistical analysis of the data was performed with SAS version 9.3 (SAS Inc., Cary, North Carolina). The chi-square test was used for comparisons of categorical data and Student *t* test for continuous parameters. A Cox proportional hazards model was used to assess the predictors of any improvement in EF after adjustment for significant covariates. Univariate predictors were initially obtained, and

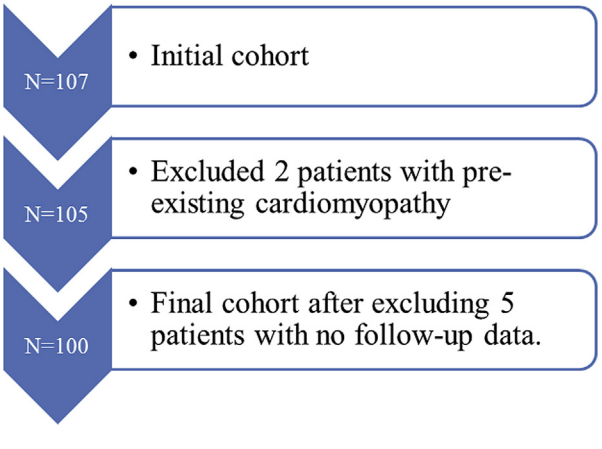

Figure 1 Flow Chart of Patient Cohort

Seven patients were excluded, which yielded a total of 100 patients in the final cohort.

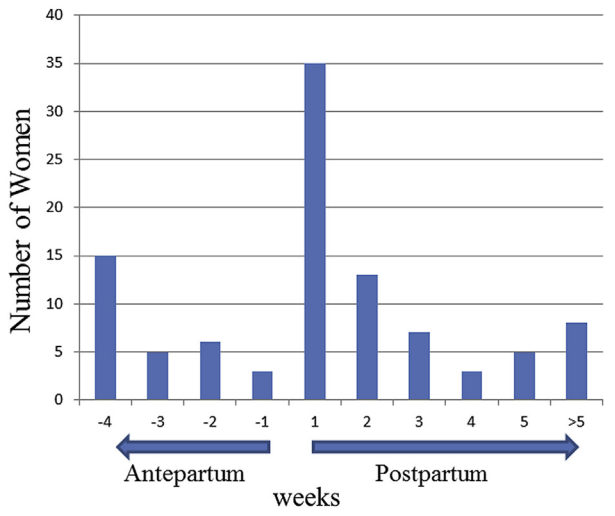

Figure 2 Time to Diagnosis of Peripartum Cardiomyopathy From Delivery

The majority of patients were diagnosed at 1 week postpartum.

if $p < 0.1$, they were included in the multivariate analysis. Baseline EF was tested both as a continuous variable and as a categorical variable (EF <30% and >30%) to determine whether it predicted recovery or mortality. Statistical significance was considered present when $p < 0.05$ in the multivariate analysis. Kaplan-Meier curves for improvement in EF and mortality were constructed for the entire population.

Results

The flow chart of cohort assembly is illustrated in Figure 1. The final cohort consisted of 100 patients with a mean age of 30 ± 6.5 years. Mean duration of follow-up for recovery of LV function was 35 ± 21 months. African Americans predominated in the sample (55%), with 39% Caucasians and 6% Hispanics.

Maternal and fetal characteristics. Preeclampsia was diagnosed in 36% of the women in the study; 61% were multiparous. The majority of patients were diagnosed after delivery (71%). The mean time to diagnosis of PPCM was 1.3 ± 4 weeks from delivery. Figure 2 shows the time to diagnosis for each patient. Forty patients had preterm delivery before 37 weeks, and tocolytic agents were used in 9. The cesarean section rate was 56%. Three women had stillbirths. The mean birth weight of the neonates was 3 ± 0.92 kg. Thirty-five women had subsequent pregnancies. Median NYHA class was III. Thirty percent of patients were in NYHA class I, 17% were in class II, 45% were in class III, and 8% were in class IV. There were 4 patients with QRS duration >120 ms at baseline. Among patients who did not recover LV function, 1 woman had a ventricular assist device implanted. Two women were listed for heart transplantation.

LV recovery. Forty-two of 100 patients (42%) had "any improvement" in EF over a mean duration of 33 ± 21 months. Of these patients, 23 had complete improvement, whereas 19 had partial recovery of LV function. Baseline

Table 1 Baseline Characteristics of All Patients

	Total (N = 100)	Improvement (n = 42)	No Improvement (n = 58)	p Value
Age, yrs	30 ± 6.5	30 ± 7	30 ± 6.2	0.7
African-American race, %	55	48	65	0.09
Baseline EF, %	28 ± 9.9	29 ± 9	28 ± 10	0.9
Diabetes mellitus, %	29	23	32	0.3
Hypertension, %	33	35	31	0.8
Gestational hypertension, %	33	33	32	0.9
Preeclampsia, %	36	40	32	0.4
Hyperlipidemia, %	9	7	10	0.6
Multiparity, %	61	52	67	0.12
Tobacco abuse, %	30	39	24	0.12
Alcohol, %	11	14	8	0.3
Cesarean section, %	56	59	54	0.46
Family history of cardiomyopathy, %	13	14	12	0.7
Left atrium enlarged, %	64	64	63	0.9
Postpartum diagnosis, %	71	83	62	0.02
QRS duration, ms	85 ± 18	83 ± 21	86 ± 16	0.4
Creatinine, mg/dl	0.8 ± 0.7	0.82 ± 0.2	0.9 ± 0.9	0.6
Hemoglobin, mg/dl	10.7 ± 1.7	10.7 ± 1.5	10.8 ± 1.8	0.6
Beta-blocker, %	82	89	78	0.2
ACEI/ARB, %	85	83	86	0.7

Values are mean ± SD or %.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; EF = ejection fraction.

Table 2 Distribution of Baseline EF Against Follow-Up EF

	Follow-Up EF				
Baseline EF	<20%	20%–30%	31%–50%	>50%	Improved (per Study Definition)
<20%	8	2	2	1	3/13 (23)
20%–30%	10	7	12	13	22/42 (52)
31%–50%	7	13	16	9	17/45 (38)

Values are n or n (%).
EF = ejection fraction.

characteristics of patients with and without improvement in EF are shown in Table 1. The distribution of baseline EF versus follow-up EF is shown in Table 2. The mean baseline EF was 28 ± 9.9%. The mean EF at follow-up for the entire group was 34 ± 18% during a mean follow-up of 35 ± 21 months. Figure 3 demonstrates the range of improvement in EF that occurred with different baseline EFs of <20%, 20% to 30%, and >30%.

In women who had any improvement (partial or complete) in LV function, the mean baseline EF was 29 ± 8%, and the mean follow-up EF was 52 ± 5%. The mean baseline EF in patients with complete recovery was 30 ± 9%, and the mean follow-up EF was 56% over a mean of 26 ± 22 months. Among these women, only 4 had complete improvement within 6 months. Delayed complete recovery beyond 6 months was noted in 83% (19 of 23 patients). The mean baseline EF in patients with partial improvement was 30 ± 9%, and the mean follow-up EF was 48%, which was achieved after a mean of 40 ± 17 months. Univariate and multivariate analysis of predictors of LV recovery (any improvement) revealed that race (Caucasian and Hispanic) and postpartum diagnosis were predictors of LV recovery, whereas there was a trend for no improvement in LV function in patients with diabetes mellitus (see Table 3 for multivariate predictors). A Kaplan-Meier curve for recovery of LV function is shown in Figure 4.

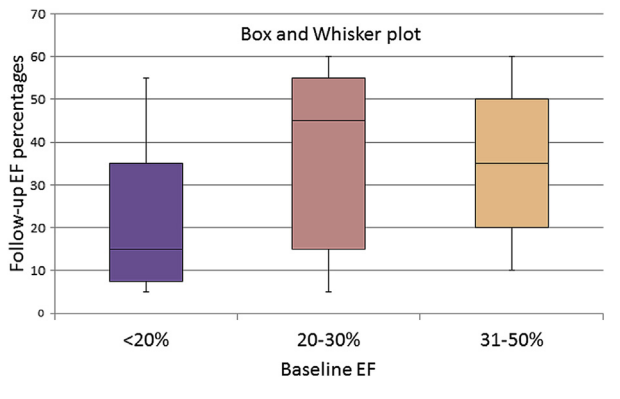

Figure 3 Follow-Up Ejection Fraction Versus Baseline Ejection Fraction

Median ejection fraction (EF) with range **(vertical bar)** and first and third quartiles **(box)** noted at follow-up in patients with baseline EF >20%, 20% to 30%, and 31% to 50% at diagnosis.

Mortality. The majority of the women were treated with optimal therapy for heart failure (beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). There was no difference in the use of beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers among patients with or without recovery of LV function (Table 1). Eleven women died during an mean follow-up of 98 ± 33 months. Nine were in the group that did not experience recovery of LV function. The mean time from last follow-up echocardiogram to death was 13 ± 12 months. In the 2 patients who improved but died, mean time to improvement was 23 months. Mortality occurred at a mean of 83 ± 1.4 months in these 2 patients. There was a trend toward higher mortality in the group that did not recover LV function (15% vs. 5%; p = 0.09). Only 1 had an ICD but died of intractable heart failure. Two other women died of arrhythmic causes, whereas the cause of death was unknown in the other 8 patients. A Kaplan-Meier survival curve for both groups is shown in Figure 5. The 5 patients with no follow-up data who were excluded from the study are noted to be alive.

ICD use. Thirteen women had ICDs implanted at some point, including 2 with CRTDs. Six women among the 42 who had complete recovery from PPCM (14%) received an ICD early in their follow-up, whereas 7 devices were present in the group without any EF improvement (n = 7 of 58; 12%). Fifty-four of the 58 patients who did not recover had an EF ≤35%, of whom 53 (1 patient was in NYHA class IV) qualified for an ICD device for primary prevention of sudden cardiac death; only 7 (13%) had a device implanted. An ICD was implanted for primary prevention in 12 patients and for secondary prevention in 1 patient.

Outcome in subsequent pregnancy. Four of the 35 women who had subsequent pregnancies died (11%). Mean

Table 3 Multivariate Predictors of LV Recovery

Predictors	Hazard Ratio	95% Confidence Interval	p Value
Race (African American vs. other)	0.45	0.2–0.8	0.01
Postpartum diagnosis	3.0	1.2–7.0	0.01
Diabetes mellitus	0.4	0.2–1.0	0.06

LV = left ventricular.

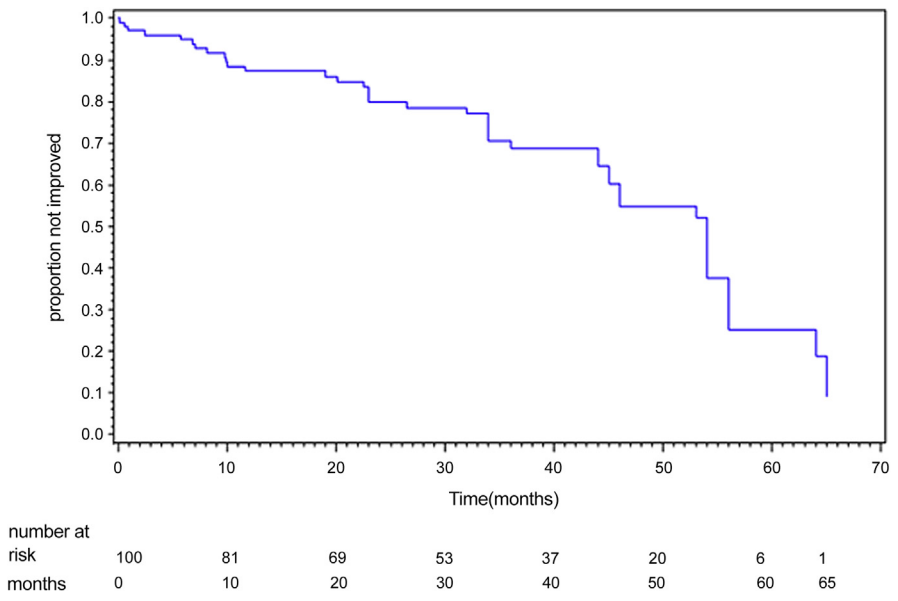

Figure 4 **Improvement in Ejection Fraction**

Kaplan-Meier curve showing proportion of patients whose ejection fraction improved over time.

baseline EF in these patients was 28 ± 10%, and follow-up EF was 30 ± 18% after a mean follow-up period of 36 ± 17 months. There was a high rate of fetal loss (36%; n = 12 of 35).

African-American versus Caucasian/Hispanic women. Table 4 shows the distribution of baseline characteristics in African-American and Caucasian/Hispanic women. There was no difference in the time to diagnosis in either group

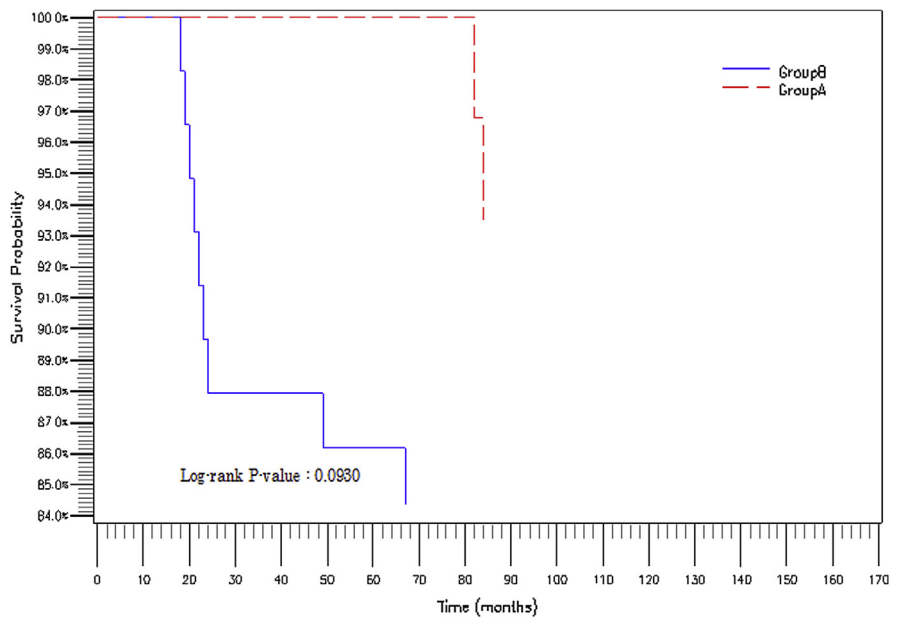

Figure 5 **Kaplan-Meier Survival Curve for Those Who Improved (Group A) and Those Without Improvement (Group B)**

Kaplan-Meier estimates were used to calculate the mortality rates in patients with and without improvement in ejection fraction.

Table 4 Differences in Baseline Characteristics on the Basis of Race

	Caucasian + Hispanic (n = 39 + 6)	African American (n = 55)	p Value
Age, yrs	30 ± 7	30.4 ± 6	0.76
Diabetes mellitus, %	20	36	0.07
Hypertension, %	37	29	0.35
Gestational hypertension, %	46	21	0.008
Preeclampsia, %	53	21	0.001
Hyperlipidemia, %	11	7	0.5
Multiparity, %	48	70	0.024
Tobacco abuse, %	24	34	0.27
Alcohol, %	8	12	0.002
Cesarean section, %	70	45	0.09
Family history of cardiomyopathy, %	11	14	0.6
Left atrium enlarged, %	58	49	0.84
Postpartum diagnosis, %	80	63	0.07
QRS duration, ms	81 ± 17	87.6 ± 18.0	0.13
Creatinine, mg/dl	0.8 ± 0.1	0.9 ± 1.0	0.4
Hemoglobin, mg/dl	10.6 ± 1.7	10.8 ± 1.7	0.5
Beta-blocker, %	95	65	0.002
ACEI/ARB, %	92	74	0.13
Baseline EF, %	27.6 ± 9.0	30.0 ± 9.8	0.2

Values are mean ± SD or %.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker.

(1.7 ± 5 weeks vs. 0.96 ± 4 weeks; p = 0.4). Mean EF at follow-up was 36.3 ± 18% in Caucasian/Hispanic women and 32 ± 17.7% in African-American women (p = 0.2). Fifty-one percent of Caucasian/Hispanic women improved compared with 34% of African-American women (p = 0.09) during a mean of 24 ± 20 months versus 44 ± 16 months (p = 0.001). Caucasians appeared to have a lower mortality, but the difference was not statistically significant (4% [2 of 45] vs. 16% [9 of 55]; p = 0.10). There was no difference in the time to death (13 ± 35 months vs. 32 ± 32 months; p = 0.42) or the use of ICDs between both groups (11% vs. 14%; p = 0.6).

Discussion

The major findings of our study are as follows. 1) A substantial proportion of patients with PPCM recover LV function (42%); complete recovery occurred in 23% of patients in the present study. 2) Our follow-up duration was long enough to note delayed complete recovery of EF beyond 6 months in the majority of the Caucasian and African-American patients (83%). 3) The present study underlines the high mortality rate (11%) in these young women. 4) This is one of the first studies to address the use of ICDs and suggests their underimplantation according to guidelines.

PPCM is distinct from other types of cardiomyopathy, although the symptoms resemble those of dilated cardiomyopathies. Oxidative stress, genetic susceptibility, autoimmunity, and myocarditis have all been implicated in the pathogenesis (1,2). Complete recovery of ventricular function may occur in a substantial proportion of women, which is unusual in other forms of cardiomyopathy (6). Complete recovery was seen in 23% of patients in the present study, with partial recovery in 19%. Other studies have reported complete recovery rates between 20% and 60% (21–29). Factors predictive of recovery suggested in prior studies included baseline ejection fraction ≥30% and LV end-diastolic diameter <5.5 cm (22,24–26). All of these studies were from single centers and involved fewer than 55 patients with limited follow-up, and none of the studies were controlled for other covariates. The present study is one of the largest studies in the United States with clinical and echocardiographic variables that were included in the model, unlike the study by Goland et al. (29), which primarily assessed echocardiographic predictors. A recent prospective study by McNamara et al. (30) that followed 100 patients in the United States showed complete recovery in 65% of women at 6 months and demonstrated that baseline EF and race were predictors of recovery and outcomes. That study, however, was limited by 6 months of follow-up. In the present study, Caucasians had a better recovery rate and earlier recovery than African-American women (24 months vs. 44 months), but baseline EF was not a predictor. A recent report of 176 South African patients with PPCM followed up for only 6 months concluded that older age and lower LV end-systolic diameter, but not EF, predicted recovery (27); however, this may not be applicable to our patient group given the racial and genetic differences. We did not find age to be a predictor but did confirm that race and postpartum diagnosis were predictors. The differences may also be explained by our longer follow-up duration, because

delayed recovery of EF beyond 6 months has been reported in 3 other recent studies (18,31,32). Biteker et al. (31) noted that only 14% of Turkish women had EF recovery in the first 6 months, whereas another 33% of women recovered beyond 6 months. Modi et al. (18) reported a median time to recovery of 54 months in African-American women in the United States, whereas Fett et al. (32) followed 32 PPCM patients in Haiti and found that the mean duration to LV recovery was 35 months. This is important to note because some have concluded that EF recovery occurs in the first 6 months and that persistence of LV dysfunction beyond 6 months is a marker of worse survival (2). In the present study, complete recovery of EF within 6 months was seen in only 4 patients (17%), whereas delayed recovery occurred in 83% of patients. To the best of our knowledge, the present study is the first to note delayed recovery of EF in Caucasian women with PPCM. The Kaplan-Meier curve in Figure 4 shows a 10% nonrecovery rate after 5 years. Long-term follow-up of these patients is thus needed, and serial clinical and echocardiographic assessments of LV function recovery should be made.

Predictors of LV recovery in our study were race and postpartum diagnosis, as was suggested previously in other studies (23,33). There are several possible reasons why an antepartum diagnosis could represent a worse outcome. Early presentation could represent more severe disease. Treatment with optimal heart failure medications is limited during pregnancy at a stage when therapy is needed the most. It is also possible that these women had subclinical PPCM with a prior pregnancy that remained undiagnosed and had progressed to become clinically manifest in the antepartum stage of the subsequent pregnancy. There was a trend for worse outcomes in patients with diabetes mellitus. This association was not reported previously with PPCM but is true in the case of structural heart disease. Prior studies were small, and few included clinical variables. With the rising incidence of diabetes mellitus in the young patient group, this association may have now become evident.

There was no difference in maternal mortality in our study in women who had a subsequent pregnancy (4 of 35 vs. 7 of 65); however, fetal mortality was high at 36%, which is similar to the 40% rate described by Modi et al. (18). This is in contrast to no perinatal mortality reported by Elkayam et al. (15). Similarly, the high cesarean section rate of 56% noted in our study was also reported in other studies (15,25,34). A cesarean section rate of 32% was reported by Elkayam et al. (25), for which obstetric pathogenesis was stated to be a reason in 70%, there was a cardiac cause in 10%, and the cause was unknown in 20%.

Therapy for heart failure consists of optimal medical management and an ICD/CRTD for primary prevention of sudden cardiac death (20). More than 80% of the patients in our study were taking beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Small studies that predated guideline-driven heart failure therapy have reported higher mortality rates (9). Recent studies in the current era, including the present study, show better outcomes (22,34). Some new therapies currently under investigation are pentoxifylline and bromocriptine (34–36). A very recent prospective study evaluated treatment with bromocriptine and suggests potential benefit in the European population (34). Cardiac resynchronization therapy has also been shown to be effective in this patient group (37).

Device therapy for primary prevention of sudden cardiac death in patients with PPCM was not specifically addressed in the 2008 device therapy guidelines (38). The present study suggests that implantation of devices in this patient group is low. Another study reported that 7 of 182 patients with PPCM had ventricular arrhythmias and underwent ICD implantation in a tertiary hospital in California; 3 of the ICDs were CRTDs (39). Similarly, 3 of 14 patients without improvement underwent ICD implantation in a recent prospective study in Europe during a follow-up of 6 ± 3 months (34). The reasons for the low implantation rates of ICDs in our study are not very clear, but possible reasons include lack of specific guidelines on the use of ICDs in PPCM patients, socioeconomic factors, patient compliance, access to long-term follow-up care, and possible follow-up by physicians other than cardiologists who are probably not very familiar with the device indications for primary prevention of sudden cardiac death.

The need and the optimal time for device implantation in women with PPCM is difficult to state, because even though delayed EF recovery may occur, the risk of sudden death before recovery remains a concern. Even though the cause of death was primarily undetermined in the present study, it seems only logical that most of these young people could have died at home of sudden cardiac arrest, because death due to decompensated heart failure would have occurred in the hospital. Baseline EF was not shown to be a predictor of recovery of LV function in the present study or a few others (4,23,27). Although EF was a predictor of improvement in a study by Goland et al. (29), they concluded that baseline EF would not be useful as a marker for early implantation of ICDs because it had limited sensitivity in predicting a lack of EF improvement. The largest epidemiological study to date of 680 PPCM patients in North Carolina reported a high mortality rate of 16% in these young women (40). We thus opine that patients with PPCM should undergo ICD implantation if no improvement is detected within the first 3 to 6 months. On the other hand, we could argue that premature implantation of ICDs in this patient group, in which the majority of patients recover, could be harmful. Subcutaneous ICDs may thus have a role in this patient group, with the advantage of not having an endovascular system and the subsequent issues related to device extraction, especially in those with clinical improvement in patients who had a continued indication for primary prevention cease to exist (41,42). Alternatively, life vests can also be used as a bridge to recovery or as a bridge to ICD if the nursing mother may find it convenient (43).

Study limitations. This was a retrospective study with a reasonable size. The exact cause of death was not available for all patients; thus, the survival benefit of ICDs could not be demonstrated in our study. Furthermore, even though the majority of patients were taking guideline-directed medications for heart failure, we do not know whether they were taking optimal doses. Given the retrospective nature of the study, we do not have information regarding why asymptomatic patients in NYHA class I underwent an echocardiographic assessment that led to the diagnosis.

Conclusions

In the present study, 42% of the women with PPCM had improvement in their LV function, with delayed recovery (>6 months) noted in the majority. Caucasians/Hispanics and those diagnosed during the postpartum period appeared to have the highest recovery rates. Our study suggests that ICD implantation rates for primary prevention of sudden cardiac death in this patient group are low, and future studies should address the utility of ICD and cardiac resynchronization therapy in these women.

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Key Words: cardiomyopathy ■ implantable cardioverter-defibrillator ■ peripartum.